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| 09/618,380 | 07/18/2000 | J. Yun Tso | 11823-004920US | 9002 |

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| EXAMINER | |
|---|---|
| HELMS, LARRY RONALD | |
| ART UNIT | PAPER NUMBER |
| 1642 | 7 |

DATE MAILED: 12/11/2001

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. 09/618,380 | Applicant(s) TSO, J. YUN | |
|---|---|---|---|
| | Examiner Larry R. Helms | Art Unit 1642 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Peri d for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) 34-42 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 34-42 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Pri rity under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: NOTICE TO COMPLY WITH SEQUENCE RULES

## DETAILED ACTION

1. Claims 1-33 have been canceled.

Claims 34-42 are pending and under examination.

2. NOTE: It is noted that the application was filed with a request to delete inventors George Weiner, Roger Gingrinch, and Brian Link, however, the application only lists one inventor, J. Yun Tso and the declaration only lists J. Yun Tso as the inventor. Therefore, the request to delete inventors is moot in view of the above.

### *Information Disclosure Statement*

3. The Information disclosure statement filed 7/18/00 has been considured as far as all U. S. Patents and references 10-12, 14, 22, 23, 30, and 33 are concerned. Application 08/397,411 did not contain the rest of the references. It is requested that Applicant submit those references not found in the prior application and the references will be considured at that time.

### *Specification*

4. The disclosure is objected to because of the following informalities:

a. The first line of the specification should be updated to indicate that the instant application claims benefit as a CON of 08/397,411, filed 3/01/95, now U.S. Patent 6,129,914 which is a CIP of 07/859,583, filed 3/27/92, now abandoned.

b. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

c. The application is objected to because of alterations which have not been initialed and/or dated as is required by 37 CFR 1.52(c). It is noted that Figures 5A and 5B have been altered by adding letters under the underlined letters. A properly executed oath or declaration which complies with 37 CFR 1.67(a) and identifies the application by application number and filing date is required.

Appropriate correction is required.

***Sequence Requirements***

5. It is noted that sequences have been added to Figures 5A and 5B as indicated above. It is also noted that the sequence added under CDR 2 of Figure 5B is different from that underlined. This sequence is required to have a SEQ ID No along with any other sequences listed in the specification that require SEQ ID Nos.

As such a notice to comply is included. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). However, as indicated above this application fails to comply with the requirements of 37 C.F.R. §§ 1.821-1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

Any questions regarding compliance with the sequence rules requirements specifically should be directed to the departments listed at the bottom of the Notice to Comply.

APPLICANT IS GIVEN THE TIME ALLOTTED IN THIS LETTER WITHIN WHICH TO COMPLY WITH THE SEQUENCE RULES, 37 C.R.F. §§ 1.821-1.825. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 C.F.R. § 1.821(g). Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 C.F.R. § 1.136. In no case may an applicant extend the period for response beyond the six month statutory period. Direct the response to the undersigned. Applicant is requested to return a copy of the attached Notice to Comply with the response.

***Drawings***

6. The drawings are objected to because Figures 5A and 5B contain alterations in the Figures by adding letters under the underlined sequences. A proposed drawing correction or corrected drawings are required in reply to the Office action to avoid abandonment of the application. The objection to the drawings will not be held in abeyance.

***Claim Objections***

7. Claim 41 is objected to because of the following informalities: Claim 41 should include the phrase "(upper lines)" after the term "5B". Appropriate correction is required.

***Claim Rejections - 35 USC § 112***

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 40 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claim 40 is indefinite as being structured as an improper Markush claims, by recited "selected from the group H30, H67, H68, H70, H72, and H74". (See MPEP 2173.05(h)). Proper Markush claims are in the format of "X is selected from a group consisting of A, B, C, and D," or "the X is A, B, C or D".

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claim 42 is rejected under 35 U.S.C. § 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention, because the specification does

not provide evidence that the claimed biological materials are (1) known and readily available to the public; (2) reproducible from the written description.

It is unclear if a cell line which produces an antibody having the exact chemical identity of M291 is known and publicly available, or can be reproducibly isolated without undue experimentation. Therefore, a suitable deposit for patent purposes is suggested. Without a publicly available deposit of the above cell line, one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed. Exact replication of: (1) the claimed cell line; (2) a cell line which produces the chemically and functionally distinct antibody claimed; and/or (3) the claimed antibody's amino acid or nucleic acid sequence which encompasses the light and heavy chain and constant regions is an unpredictable event.

For example, very different $V_H$ chains (about 50% homologous) can combine with the same $V_K$ chain to produce antibody-binding sites with nearly the same size, shape, antigen specificity, and affinity. A similar phenomenon can also occur when different $V_H$ sequences combine with different $V_K$ sequences to produce antibodies with very similar properties. The results indicate that divergent variable region sequences, both in and out of the complementarity-determining regions, can be folded to form similar binding site contours, which result in similar immunochemical characteristics. [FUNDAMENTAL IMMUNOLOGY 242 (William E. Paul, M.D. ed., 3d ed. 1993)]. Therefore, it would require undue experimentation to reproduce the claimed antibody species M291. Deposit of the hybridoma would satisfy the

enablement requirements of 35 U.S.C. § 112, first paragraph. See, 37 C.F.R. 1.801-1.809.

If the deposit is made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney of record who has authority and control over the conditions of deposit over his or her signature and registration number stating that the deposit has been accepted by an International Depository Authority under the provisions of the Budapest Treaty and that all restrictions upon public access to the deposited material will be irrevocably removed upon the grant of a patent on this application. This requirement is necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State.

If the deposit is not made under the provisions of the Budapest Treaty, then in order to certify that the deposits comply with the criteria set forth in 37 CFR 1.801-1.809 regarding availability and permanency of deposits, assurance of compliance is required. Such assurance may be in the form of an affidavit or declaration by applicants or assignees or in the form of a statement by an attorney of record who has the authority and control over the conditions of deposit over his or her signature and registration number averring:

(a) during the pendency of this application, access to the deposits will be afforded to the Commissioner upon request:

(b) all restrictions upon the availability to the public of the deposited biological material will be irrevocably removed upon the granting of a patent on this application:

(c) the deposits will be maintained in a public depository for a period of at least thirty years from the date of deposit or for the enforceable life of the patent of or for a period of five years after the date of the most recent request for the furnishing of a sample of the deposited biological material, whichever is longest; and

(d) the deposits will be replaced if they should become nonviable or non-replicable.

Amendment of the specification to recite the date of deposit and the complete name and address of the depository is required. As an additional means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

If a deposit is made after the effective filing date of the application for patent in the United States, a verified statement is required from a person in a position to corroborate that the biological material described in the specification as filed is the same as that deposited in the depository, stating that the deposited material is identical to the biological material described in the specification and was in the applicant's possession at the time the application was filed.

Applicant's attention is directed to In re Lundak, 773 F.2d. 1216, 227 USPQ 90 (CAFC 1985) and 37 CFR 1.801-1.809 for further information concerning deposit practice.

12. Claim 42 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a humanized antibody comprising a heavy chain

and a light chain wherein the heavy chain comprises three CDRs from the mouse M291 heavy chain of SEQ IS NO:11 and a light chain that comprises three CDRs from the mouse M291 light chain of SEQ ID NO:9, does not reasonably provide enablement for any humanized form of the mouse M291 antibody. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The claim is broadly drawn to any humanized form of the mouse M291 antibody. The claim broadly encompasses antibodies which do not contain a full set of CDRs from each of the heavy chain and the light chain of SEQ ID NO:11 and 9. The claim broadly encompasses antibodies that do not bind the CD3 antigen.

The specification teaches humanization of the mouse M291 antibody wherein all 6 CDRs from the M291 light chain and heavy chain are substituted into human framework regions and the antibody binds CD3 (see example 4). The specification does not enable a humanized antibody that does not contain all 6 CDRs from the mouse M291 antibody or a humanized antibody that does not bind antigen of CD3.

It is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc Natl Acad Sci USA 1982 Vol 79 page 1979). Rudikoff et al. teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. It is unlikely that antibodies as defined by the claims which may contain less than the full complement of CDRs from the heavy and light chain variable regions of an M291 antibody in unspecified order, have the required binding function. The specification provides no direction or guidance regarding how to produce antibodies as broadly defined by the claims. Undue experimentation would be required to produce the invention commensurate with the scope of the claims from the written disclosure alone.

Therefore, in view of the lack of guidance in the specification, the breadth of the claim, and in view of the unpredictability in the art as evidenced by Rudikoff et al , one of skill in the art would be required to perform undue experimentation in order to practice the claimed invention.

***Double Patenting***

13. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

14. Claims 34-42 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 15-17 of U.S. Patent No. 6,129,914 in view of Queen et al (U. S. Patent 5,693,762, with priority as a CON to 12/19/90). Although the conflicting claims are not identical, they are not patentably distinct from each other. The claims in the instant application are broader than those in U. S. Patent 6,129,914. Specifically the claims in the patent encompass species of H30, H67, H68, H70, H72, and H74 and the claims in the instant application are drawn

to a humanized antibody comprising CDRs from the mouse M291 antibody wherein one or more framework residues which interact with the CDRs are optionally substituted and a humanized form of the M291 mouse antibody. The claims in 6,129,914 are drawn to humanized M291 antibodies wherein specific residues H30, H67, H68, H70, H72, and H74 are substituted in the human framework region for mouse residues and does not claim a substitution of any residue that interacts with a CDR. The claims in the instant application are broader in that they encompass substitutions of any residue that interacts with a CDR.

It would have been obvious to humanize the M291 antibody and substitute framework residues that interact with the CDRs in view of Queen et al.

One would have been motivated to and has a reasonable expectation of success to have to humanize the M291 antibody and substitute framework residues that interact with the CDRs in view of Queen et al because Queen et al specifically teach substitution of residues in the framework with mouse residues if they interact with a CDR (see column 3, lines 14-18) and in Example 9 a humanized antibody was produced with alterations in the residues that were predicted to interact with a CDR.

Therefore, it would have been obvious to humanize the M291 antibody and substitute residues that interact with a CDR in order to retain antigen binding as taught by Queen et al.

Claims 34-42 are directed to an invention not patentably distinct from claims 15-17 of commonly assigned U.S. Patent 6,129,914. Specifically, see above.

Commonly assigned U. S. Patent 6,129,914, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee is required under 37 CFR 1.78(c) and 35 U.S.C. 132 to either show that the conflicting inventions were commonly owned at the time the invention in this application was made or to name the prior inventor of the conflicting subject matter. Failure to comply with this requirement will result in a holding of abandonment of the application.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g).

***Conclusion***

15. Claims 34-42 are free of the prior art. The closest prior art is that of Jolliffe et al (WO 91/09968, published 7/11/91. Jolliffe et al teach an antibody OKT3 which binds the same antigen as M291 but has different CDRs as shown in Figures 1B and 2B. Thus, Jolliffe et al does not teach or fairly suggest the sequences of the light and heavy chain variable region of M291 or the CDRs of the light and heavy chain of M291.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D, whose telephone number is (703) 306-5879. The examiner can normally be reached on Monday through Friday from 7:00 am to 4:30 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

17. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 308-4242.

Respectfully,

Larry R. Helms Ph.D.

703-306-5879